PHYTOTHERAPY RESEARCH
Phytother. Res. **18**, 700–705 (2004)
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI**: 10.1002/ptr.1511

Herbal Treatment Following Post-seizure Induction in Rat by Lithium Pilocarpine: *Scutellaria lateriflora* (Skullcap), *Gelsemium sempervirens* (Gelsemium) and *Datura stramonium* (Jimson Weed) May Prevent Development of Spontaneous Seizures

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About 1 week after the induction of status epilepticus in male rats by a single systemic injection of lithium (3 mEq/kg) and pilocarpine (30 g/kg), rats were continuously administered one of three herbal treatments through the water supply for 30 days. A fourth group received colloidal minerals and diluted food grade hydrogen peroxide in tap water, while a fifth group of rats received only tap water (control). Herbal treatments were selected for their historical antiseizure activities and sedative actions on the nervous system. The numbers of spontaneous seizures per day during a 15 min observation interval were recorded for each rat during the treatment period and during an additional 30 days when only tap water was given. Rats that received a weak solution of the three herbal fluid extracts of *Scutellaria lateriflora* (Skullcap), *Gelsemium sempervirens* (Gelsemium) and *Datura stramonium* (Jimson Weed) displayed no seizures during treatment while all the other groups were not seizure-free. However, when this treatment was removed, the rats in this group displayed numbers of spontaneous seizures comparable to the controls. Although there is no proof that herbal remedies can control limbic or temporal lobe epilepsy, the results of this experiment strongly suggest that the appropriate combination of herbal compounds may be helpful as adjunctive interventions. Copyright © 2004 John Wiley & Sons, Ltd.

Keywords: anti-seizure herbal treatments; *Scutellaria lateriflora*; *Gelsemium sempervirens*; *Datura stramonium*.

INTRODUCTION

The development of the lithium/pilocarpine limbic seizure model in the rodent has been instrumental in bringing researchers closer to an understanding of the physical and neurological mechanisms that underlie human temporal lobe epilepsy. Temporal lobe epilepsy is a manifestation of the episodic synchronous discharges in electrically labile nerve cells within the hippocampus and amygdala. These structures are intimately connected with the limbic system, which harbors neuroanatomical substrates that are involved in the expression of behaviors essential for self-preservation. Progressive neurological degeneration from sustained seizure activity has produced a spectrum of behaviors ranging from conditioned taste aversion (Venugopal and Persinger, 1988) and spatial memory deficits (Harrigan *et al*., 1991) to aggressiveness (Bedard and Persinger, 1995) and dysfunctional male sexual behavior (Persinger, 1994) and dysfunctional maternal behavior (Peredery *et al*., 1992).

Past studies have utilized both non-pharmacological substrates such as electromagnetic fields (Bureau and Persinger, 1995) and pharmaceutical agents (Bureau and Persinger, 1993; Harrigan *et al*., 1995) in an attempt to attenuate either the time of seizure onset or the intensity of the ensuing behaviors. Behavioral pharmacology has emphasized the creation of highly specialized and pure compounds to affect very specific behaviors. To date, each pharmacological agent or drug was chosen for its singular effect, its administration an attempt to attenuate the relatively holistic and complex effects of seizure activity. If it is considered that complex behaviors are correlated with neurotransmitter-mediated chemical interactions within a neuromatrix, the brain, then a matrix approach would suggest that some behaviors might simultaneously involve a large number of receptors. The emergent antithesis to extreme 'specificity' of pharmacological intervention has been treatment by herbal preparations that consist of natural chemical matrices.

Thus, to examine broad-spectrum neuropharmacological effects on seizure activity, a holistic approach was taken for this study. This alternative approach involved the use of traditional botanical herbs historically known to have anticonvulsant, sedative and tonic properties (Ellingwood, 1919), and colloidal minerals that by their nature promote a drive towards homeostasis in an organism (Wallach and Lan, 1996). It is well known that the therapeutic effects and the

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Contract/grant sponsor: Laurentian University Research Fund.

Received 4 August 2003
Accepted 21 April 2004

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lack of side effects of botanical herbs depend upon their unique biochemical matrix, and the synergistic actions of the multiple constituents within each herb (Hoffman, 1991; Serrentino, 1991). These effects are often difficult to mimic with a single, isolated pharmaceutical substance (Heinermann, 1984; Mills, 1993).

The abrupt shift towards excitotoxicity that occurs due to seizure activity produces sudden changes in the levels of physiological compounds (i.e. phosphates, oxygen, glucose) and ionic concentrations at the cellular level (Lennox, 1960). Readily absorbable ions in the form of tonics and colloidal minerals may provide the substrates necessary to compensate for those utilized during excitotoxicity and thus aid in attenuating damage resulting from seizure activity (Fukahori and Itol, 1990; Maki *et al.*, 2002). In contrast to single, highly pure substances, the unique properties of botanical herbs, tonics and colloidal minerals render them less concentrated and less likely to cause functional tolerance and habituation because of the greater number of different receptors that would be involved. Because the induced lithium/pilocarpine seizure produces diffuse neurodegeneration affecting areas of the brain that are concerned with a variety of behaviors, it was proposed that the administration of alternative substances that include a broader spectrum of pharmacological effects should influence and possibly attenuate seizure activity to a greater degree than would be expected from a single drug constituent. These effects may be evident through the measure of 'spontaneous seizures'.

METHODOLOGY

A total of 35 90-day-old Wistar rats, obtained from Charles River (Quebec) were injected with 3 mEq/kg of lithium followed 24 h later with 30 mg/kg of pilocarpine. Immediately after the onset of seizures, the rats were injected subcutaneously with 25 mg/kg of acepromazine (Atravet). About 6 h later, they were injected subcutaneously with 1 mg/kg of atropine to minimize residual salivation. The rats were then placed in single wire cages, and given food mush and water to facilitate recovery.

One week after seizure induction the rats were randomly assigned to one of five treatment groups (7/treatment). The first treatment group consisted of tap water (control). Subsequent treatment groups received, in their drinking water, a concentration (based on weight) of one of the following treatments: group 2: Kombucha tea; group 3: colloidal minerals (*Liquid Essence* by New Vision) + hydrogen peroxide (*Peroxysan*); group 4: anticonvulsant herbal formula 1, (consisting of a cocktail of herbs historically indicated for epilepsy and/or sedative and/or tonic action on the nervous system); group 5: selected anticonvulsant/sedative herbs (Table 1). The herbs used were in the form of herbal fluid extracts (Gaia). All drinking bottles were refreshed daily, and there were no conspicuous differences (within 5cc) in the volumes consumed between the treatment groups. The rats were exposed to the treatments continuously for 30 days, after which treatments were discontinued and replaced with tap water for another 30 days. Food was available *ad libitum*.

At 17:00 daily, each rat received two Purina food cubes in its cage. This procedure, despite *ad libitum* food, is associated with eating behaviour and the elicitation of seizures. The numbers of seizures was recorded for each rat during 15 min following the food cube presentation. During the 60 days of the experiment, the number of rats that died for each for the five treatment conditions was: 1:0, 2:1, 3:0, 4:3 and 5:1. The numbers of seizures during the treatment period vs the water-only period for each of the five groups were analysed by two-way analysis of variance with one level (treatment period vs water period) repeated. All analyses involved SPSS software.

Table 1. Compounds contained within each of the five treatments. Colloidal minerals, hydrogen peroxide, and all herbs in treatment groups 4 and 5 were commercially prepared. Herbs were in the form of fluid extracts. Kombucha tea was commercially prepared

Treatment group	Herb	Volume/2 L water
1	Tap water	
2	Kombucha tea	90 ml
3	Colloidal minerals	10 ml
	3% hydrogen peroxide (food grade)	20 drops
4	*Scutellaria lateriflora* (Skullcap)	15 drops
	Verbena hasta (Blue Vervain)	24 drops
	Primula officinalis (Cowslip)	24 drops
	Gelsemium sempervirens (Gelsemium)	24 drops
	Lobelia inflata (Lobelia)	24 drops
	Passiflora incarnata (Passionflower)	24 drops
	Valerian officinalis (Valerian)	48 drops
	Datura stramonium (Jimson Weed)	24 drops
	Viscum album (Mistletoe)	24 drops
	Gentiana lutea (Gentian)	56 drops
	Capsicum frutesens (Capsicum)	15 drops
	Caudophyllum thalictroides (Blue Cohosh)	44 drops
	Cimicifuga racemosa (Black Cohosh)	32 drops
5	*Scutellaria lateriflora* (Skullcap)	15 drops
	Gelsemium sempervirens (Gelsemium)	24 drops
	Datura stramonium (Jimson Weed)	24 drops

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Table 2. Mean and standard deviations for the numbers of numbers of seizures per 15 min daily intervals during the 30 days of treatment and 30 days of water-only treatment. Numbers of rats per group that showed at least one seizure are also shown

Treatment group	n	Treatment period			Water-only period		
		M	SD	No. of rats	M	SD	No. of rats
1	7	.7	.8	4	.7	1.1	3
2	6	1.5	1.9	3	.3	.5	2
3	7	2.0	1.6	6	1.4	.0	6
4	4	2.0	2.1	3	.5	1.0	1
5	6	0	0	0	2.0	1.3	6

RESULTS

The means and standard deviations for the average numbers of spontaneous seizures as well as the number of animals per group displaying at least one seizure during the 30 day treatment period and the 30 day post-treatment (water only) are shown in Table 2. Two-way analysis of variance with one level repeated and one between-subject level (treatment) showed a statistically significant [$F(4,25) = 4.47$, $p < 0.01$; eta squared = 0.43] interaction between treatment period and treatment groups. There were no statistically significant differences between the two periods of treatments [$F(1,25) = 0.74$, $p > 0.05$] or between treatments [$F(4,25) = 1.03$, $p > 0.05$]. Square root transformations of the numbers of seizures verified the statistically significant interaction [$F(4,25) = 7.43$, $p < 0.001$; eta squared = 54% of variance explained].

Post hoc analyses with correlated *t*-tests indicated that the primary source of the interaction was due to the decrease in seizures after the fourth treatment was terminated ($t(3) = 2.32$, $p < 0.10$) but an increase in numbers of seizures when the fifth treatment was terminated ($t(5) = 3.87$, $p = 0.01$). Differences between the treatment and water-only periods for each of the other three groups did not even approach statistical significance (all $t < 1.50$). Additional post-hoc analysis between treatment groups for the square-root transformed data indicated that the rats in the fifth group displayed significantly (Student-Neuman-Keuls, $p < 0.05$) more seizures after the herb treatments were terminated, compared with either the tap water controls or the group treated with the Kombucha tea. During the treatment period, the rats that received the colloidal minerals + hydrogen peroxide showed more seizures than the rats that received the *Scutellaria*, *Gelsemium* and *D. stramonium*.

DISCUSSION

The rats that received *Scutellaria*, *Gelsemium* and *D. stramonium* did not exhibit any seizures during the 30 days of treatment. However, when this treatment period terminated, and the rats were exposed to the water-only period, seizures developed to within the range of controls from this and other studies. Interestingly, removal of the most complex herbal concoction, that contained *Scutellaria*, *Gelsemium* and *D. stramonium* combined with 10 other herbs, attenuated the numbers of seizures, but did not eliminate them.

Scutellaria, *Gelsemium* and *D. stramonium* have potent effects on the central and peripheral nervous system. *Scutellaria* leaf is reported to possess anticonvulsant and nerve sedative properties possibly mediated through GABA-A receptors (Newall *et al*., 1996; Liao *et al*., 1998). In folkloric medicine, it was used for epilepsy, chorea, paralysis agitans and delirium tremens. *Gelsemium*, in addition to its antiinflammatory properties, was also traditionally believed to have a beneficial influence in epilepsy and chorea. *Gelsemium* contains several gelsemine alkaloids that are reported to be both CNS stimulants and CNS depressants (Newall *et al*., 1996; Ellingwood, 1919). Historically, *D. stramonium* was given in small doses in epilepsy for its soothing and tranquilizing effect (Ellingwood, 1919; Grieve, 1992; Jellin, 2000). *D. stramonium* contains trace to small proportions of the solanaceous alkaloids scopolamine and atropine. However, its anticholinergic actions are chiefly due to its principle alkaloids hyoscyamine and stramonium. Hyoscyamine, although similar to atropine in its actions, has a stronger activity than atropine (Bruneton, 1995; Robbers *et al*., 1996). The synergistic actions of the combined chemical matrices in *D. stramonium*, *Scutellaria* and *Gelsemium* may have played a significant role in inhibiting the neurophysiological kindling of seizures and overt seizure activity in this treatment group.

The combination of *Scutellaria*, *Gelsemium* and *D. stramonium*, with other herbs traditionally considered as anticonvulsive and sedative (*Lobelia*, *Valerian*, *Verbena*, *Passiflora* and *Cimicifuga*. *Caudophyllum*, *Capsicum*, *Viscum*, *Gentian* and *Primula*), was also intended to produce a synergistic effect in preventing seizure activity in the animals of this treatment group. It was reported that combinations of these sedating herbs were effective in controlling spasms and choreas (*Cimicifuga*, *Scutellaria*, *Gelsemium* and *Valerian*), (*Cimicifuga* and *Passiflora*), infantile convulsions and epilepsy (*Lobelia* and *Capsicum*), (*Mistletoe*, *Valerian* and *Verbena*), as well as acting as nerve tonics (*Primula* and *Gentiana*) (Ellingwood, 1919; Grieve, 1992; Newall *et al*., 1996; Jellin, 2000). None of these herbs negatively interacted with one another (Brinker, 1998). It is recognized that the chemical complexity within a plant matrix leads to enhanced bioavailability, improved stability, and possibly increased half-life of the active key components. In terms of the chemical complexity that makes up the plant, the action of the chemical mixture is greater than the arithmetical sum of the

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actions of the mixture's components (Mills and Bone, 2000). Thus, in the context that the whole is greater than the sum of the individual parts, it was expected that this chemically complex repertoire would be sufficient to eliminate pharmacologically induced seizure kindling and overt seizure activity. However, only a reduction in the number of overt seizures was observed. This treatment group also exhibited a higher death rate compared with other treatment groups. Suggested variables that could possibly be implicated, and would require further study would be the hepatic and renal abilities of pharmacologically induced seizured animals to clear a complex chemical mixture, and the ratio of predominantly anticonvulsant herbs to sedative herbs or to nervines.

Kombucha tea and the mixture of colloidal minerals and hydrogen peroxide were selected as trophorestoratives in the 2nd and 3rd treatment arms, respectively (Kaufmann, 1995; Wallach and Lan, 1996). It is understood that seizures produce unusually sharp fluctuations in the internal environment of an organism (Carl *et al*., 1990). Maintenance of acidic internal environments (i.e. with ketogenic diets) has proved instrumental in attenuating seizures (Hori *et al*., 1997). Kombucha tea (consisting of *Acetobacter xylinum*, *Aygosaccharomyes* and *Saccharomyces cerevisiae* microorganisms, black tea components, vitamins, minerals, sugars and organic acids) was used to achieve a reduction or elimination of seizures through mild systemic acidosis in this pharmacologically induced seizure model. It has been reported that an average 9-day fermentation of Kombucha harbors 7 g/L acetic acid and an average pH of 2.5 (Currier *et al*., 1995; Greenwalt *et al*., 1998). Similarly, supplementation with colloidal minerals was utilized primarily as a source of trace minerals magnesium, manganese, zinc and selenium (Morello, 1999) in addition to copper, molybdenum, cobalt and rubidium (Maki *et al*., 2002) that was reported to be significantly deficient in epileptics. Hydrogen peroxide was included as an endogenous source of oxygen (McCabe, 1988). However, animals in either of these treatment groups did not show any significant reduction in the number of seizures between treatment periods or between treatment groups.

CONCLUSION

To the best of our knowledge, this is the first study to evaluate the effects of chemically complex, natural substances predominantly in the form of anticonvulsant and sedative herbs, and trophorestorative minerals on the development of pharmacologically induced spontaneous seizures in rats. Our research indicates that almost all (>95%) of the rats subjected to the lithium/pilocarpine seizure model achieve *status epilepticus*, and continue to exhibit spontaneous seizures throughout their lifetime, remaining dominantly parasympathetic. Consequently, an herbal combination of *D. stramonium*, *Gelsemium* and *Scutellaria*, consisting of anticholinergic, parasympathomimetic and sedative properties (presumably GABAa agonists) that prevented seizures may have done so by attenuating the neurophysiological processes that lead to kindling of seizures. This was most evident when this treatment was removed, and the seizure activity increased to baseline levels. The observation that seizure activity resumed in the post-treatment period (water-only) suggests that despite the three-herb treatment, the structural changes brought on by pharmacologically induced initial seizure activity remained and encouraged continuous seizure activity. Although this treatment was the first to actually stop the overt display of spontaneous seizures in these rats, we caution that herbal remedies alone have not been proven to control epilepsy with the same efficacy and safety as pharmaceutically derived antiepileptic compounds.

Acknowledgement

This research was supported by a grant to O. Peredery, N.D. from the Laurentian University Research Fund.

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APPENDIX

The herbs chosen for this study were based on single or combined herbs that were historically/traditionally used as agents acting on the nervous system (directly or indirectly). Specifically, those used for the treatment of epilepsy, and/or convulsions of nervous disorders were chosen.

Detailed actions of herbs used in this study

Kombucha tea	Trophorestorative, nutritive
Colloidal minerals + 3% hydrogen peroxide	Trophorestorative, nutritive
HERB	**ACTIONS**
Direct/indirect action on nervous system	
Scutellaria laterifolia (Skullcap) [direct]	Neurotrophic, trophorestorative, antispasmodic, sedative, tonic, nervine (Santillo, 1993); GABA-A agonist (Liao *et al*., 1998)
Verbena hasta (Blue Vervain) [direct]	Antispasmodic, sedative, hypnotic, diaphoretic, hepatic, hypotensive (Hoffman, 1990): increases O_2 to the brain (Heinermann, 1984); parasympathomimetic (Kenner and Requena, 1996)
Primula officinalis (Cowslip) [direct]	Sedative, antispasmodic, neurotrophic (Grieve, 1992)
Gelsemium semervirens (Gelsemium) [direct]	Antispasmodic, tranquillizer, vasodilator, analgesic (Bartram, 1998); antiinflammatory, antipyretic, antiepileptic, antichoreic (Ellingwood, 1919) parasympathomimetic (Kenner and Requena, 1996)
Lobelia inflata (Lobelia; Indian tobacco) [indirect]	Antispasmodic, emetic, nervine, relaxant (mild sedative in large doses), expectorant (Santillo, 1993; Hoffman, 1990); CNS stimulant and relaxant (like nicotine) (Leung and Foster, 1996); bronchodilator, antasthmatic (Bartram, 1998; Newall *et al*., 1996); DA antagonist (Teng *et al.,* 1998)
Passiflora incarnata (Passionflower) [direct]	Sympatholytic, hypnotic, tranquillizer (Kenner and Requena, 1996); antispasmodic and anodyne (Newall *et al*., 1996); antiepileptic (if used in aura stage), anti-choreic (Ellingwood, 1919); CNS-depressant, hypotensive, sedative (Hoffman, 1990); GABA-A agonist with central and peripheral effects (Medina *et al*., 1990)
Valerian officinalis (Valerian) [direct]	Antispasmodic and equalizing (sedative in states of agitation and stimulant in fatigue), hypotensive (Hoffman, 1990; Leung and Foster, 1996); sympatholytic, parasympatholytic, sedative, anticonvulsant (Kenner and Requena, 1996)
Datura stamonium (Jimson Weed) [direct]	CNS and PNS anticholinergic, hypnotic (Leung and Foster, 1996); respiratory spasmolytic, sedative, depressant, strongly parasympatholytic (Bruneton, 1995; Kenner and Requena, 1996)
Viscum album (Mistletoe) [indirect]	Antispasmodic, antiepileptic, hypotensive, anodyne (Ellingwood, 1919); antineoplastic, abortifacient, antiinflammatory (Leung and Foster, 1996); symatholytic and parasympathomimetic (Kenner and Requena, 1996)
Gentiana lutea (Gentian) [indirect]	Antiinflammatory, stomachic, (Leung and Foster, 1996); hypotensive (Bruneton, 1995); antispasmodic, digestant (Bartram, 1998); tonic, cholagogue (Santillo, 1993); parasympatholytic (Kenner and Requena, 1996)
Capsicum frutesens (Capsicum) [direct/indirect]	AchE activity, synergistic (Leung and Foster, 1996); systemic circulatory stimulant (increases O_2 to the brain), neurorestorative, antispasmodic and general relaxant (Hoffman, 1990; Ellingwood, 1919)
Caudophyllum thalictroides (Blue Cohosh) [indirect]	Antispasmodic, cerebrospinal trophorestorative (equallizing), synergistic (Hoffman, 1990); oxytocic diuretic, emmenagogue (Santillo, 1993)
Cimicifuga racemosa (Black Cohosh) [indirect]	Antispasmodic (musculotrope and neurotrope), relaxant nervine, alterative, hypotensive, antichoreic, antiepileptic (hormonally induced) (Santillo, 1993; Hoffman, 1990; Ellingwood, 1919); Sedative, sympatholytic, parasympatholytic (Kenner and Requena, 1996)

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